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PRE-APPEAL BRIEF REQUEST FOR REVIEW

Docket Number (Optional): TOPI-002CIP

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Signature _____

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Application Number	Filed
10/029,407	12/26/2001

First Named Inventor: CALDWELL, Larry

Art Unit	Examiner
1611	Ghali, Isis A.D.

Applicant requests review of the final rejection in the above-identified application. No amendments are being filed with this request.

This request is being filed with a notice of appeal.

The review is requested for the reason(s) stated on the attached sheet(s).
Note: No more than five (5) pages may be provided.

I am the

- ☐ applicant/inventor.
- ☐ assignee of record of the entire interest. See 37 CFR 3.71. Statement under 37 CFR 3.73(b) is enclosed. (Form PTO/SB/96)
- ☑ attorney or agent of record. Registration number 37,620.
- ☐ attorney or agent acting under 37 CFR 1.34. Registration number if acting under 37 CFR 1.34 _____

/Bret E. Field, Reg. No. 37,620/
Signature

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Typed or printed name

650-327-3400
Telephone number

02/11/2009
Date

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below*.

☐ *Total of _____ forms are submitted.

This collection of information is required by 35 U.S.C. 132. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11, 1.14 and 41.6. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Mail Stop AF, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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VIA ELECTRONIC FILING FEBRUARY 11, 2009

PRE-APPEAL BRIEF REQUEST FOR REVIEW	Attorney Docket No.	TOPI-002CIP
	Confirmation No.	3764
	First Named Inventor	Caldwell, Larry
	Application Number	10/029,407
	Filing Date	December 26, 2001
	Group Art Unit	1611
Address to: Mail Stop AF Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450	Examiner Name	Ghali, Isis A. D.
	Title:	*Methods and compositions for treating headache pain with topical NSAID compositions*

Sir:

This pre-appeal review is requested for the reasons outlined below.

The Applicants thank the Examiner for the withdrawal of the rejection of Claims 1-18 and 24-28 under 35 U.S.C. §112, first paragraph in the Final Office Action dated November 4, 2008.

In the Final Office Action dated November 4, 2008, the Examiner maintained the rejection of Claims 1-18 and 24-33 under 35 U.S.C. §103(a) as allegedly being obvious over the combined teachings of either Pradalier et al. or Cluff, each combined with both US 6,667,799 to Caldwell and US 5,318,960 to Toppo. The Applicants respectfully traverse this rejection.

The Applicants request that the pre-appeal conference evaluates whether: (A) the combined references actually teach or suggest all the elements of the claimed invention; (B) whether the art provides the requisite reasonable expectation of success in the claimed invention; and (C) whether the cited teachings of the art have been properly combined.

Pending Claims

Claim 1 is representative of the pending claims and is set forth below:

1. (Previously presented) A method for ameliorating headache pain caused by a tension headache, migraine headache, indomethacin responsive headache syndrome or cluster headache, said method consisting of:

topically applying an anti-inflammatory effective amount of a topical NSAID formulation comprising an NSAID as the only active agent present in said topical formulation to a keratinized skin surface of the head of said host to ameliorate said headache pain caused by a tension headache, migraine headache, indomethacin responsive headache syndrome or cluster headache.

The rejected claims specify *topically applying* an anti-inflammatory effective amount of a topical NSAID formulation to a keratinized skin surface of the head. "Topical" drug products are understood by those of skill in the art to be products that produce their clinical effect by being applied to the skin, which subsequently interact with soft tissues and nerves underlying the keratinized skin where the drug is applied. It is known by those of ordinary skill in the art that topically applied formulations do not result in clinically significant systemic blood levels, and do not produce any significant systemic side effects.[1]

The rejected claims further specify that *a non-steroidal anti-inflammatory (NSAID) agent* is *the only active agent* present in the topical formulation (i.e., there is no nerve blocking agent present).

The claims also specify that the method is a method for ameliorating headache pain caused by *a tension headache, migraine headache, indomethacin responsive headache syndrome or cluster*

[1] See Galer and Dworkin, A Clinical Guide to Neuropathic Pain (McGraw-Hill, 2000) p. 57; and Galer BS, Gammaitoni A, Alvarez, N.; Pain; Scientific American Medicine, WebMD, 2001, Chapter 10, Section XIV, p. 22; and Loeser, JD: Bonica's Management of Pain (Galer BS, "Topical Drugs for the Treatment of Pain" chapter; 2000, p. 1737; referred to in the Response to Office Action of 7-13-07, pp.8-9.

headache (i.e., headaches caused by disturbances in the central nervous system). As stated in the previously submitted declaration by Dr. Bradley Galer dated June 2, 2006,

> "In contrast, headaches such as migraine, cluster, tension headaches, and indomethacin responsive headaches (IRH) are not caused by musculoskeletal or peripheral nerve damage mechanisms, rather they are headaches that are caused by disturbances in the central nervous system [2]...Accordingly, migraine, cluster, tension headache, and IRH conditions are considered unique clinical entities distinct from those conditions of headache pains caused by localized musculoskeletal mechanisms (e.g., muscle contractions). In fact, the International Association for the Study of Pain, the world's foremost medical and scientific pain society characterizes migraine headaches as arising from central nervous system mechanisms, and not the musculoskeletal system." [3]

As such, the rejected claims require topically applying an anti-inflammatory effective amount of a topical NSAID formulation (not a nerve blocking agent) to a keratinized skin surface of the head, which works via a local anti-inflammatory mechanism (i.e., non-systemic), and is applied at a topical site which is not the site of origin of the painful condition.

Analysis

The Applicants respectfully submit that A) the combined teachings of the references fail to teach or suggest all elements of the claimed methods; B) the cited combination of references fails to provide the requisite predicted success in the claimed invention; and C) the cited prior art references have been improperly combined. These elements are discussed individually below.

A) The Applicants maintain that the combination of the references does not render the claimed invention obvious because the combination of the cited references fails to teach or suggest each and every element of the claims.

The cited prior art references of Pradalier and Cluff disclose the general use of oral NSAIDs for the treatment of migraines, a method well known in the art to provide clinically significant systemic NSAID blood levels required in order to achieve relief of headache pain; in fact it is known that a dose-response relationship exists when these drugs are given orally, that is a certain dose of the drug has to be ingested and carried into the blood stream in order to have a headache alleviating effect. Pradalier and Cluff are silent, however, with respect to topically applying a topical NSAID formulation as in the rejected claims. There is no teaching in either reference of topical administration of NSAIDs, nor is there any suggestion of topical administration of an NSAID in either reference.

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[2] See Aurora, "Pathophysiology of Migraine Headache" and Dodick, "Indomethacin-responsive Headache Syndromes." from Exhibit A, enclosed in Response to Office Action of 3-30-06.

[3] See Merskey, H, and Bogduk, N. "Classification of Chronic Pain" 2nd Edition, p. 77; submitted as Exhibit B, enclosed in Response to Office Action of 3-30-06.

Toppo is directed to NSAID compositions for relief of pain, and the only specific pain mentioned in Toppo is arthritis pain (col. 1, lines 20-25), where the area of pain experienced is also the exact site of inflammation causing the symptom of pain in the same body region. Furthermore, headache and arthritis have distinct underlying pathophysiologies and as such are studied and cared for by very different types of physician specialties, rheumatology and neurology, with distinct diagnostic evaluations and therapies. The compositions of Toppo are delivered transdermally "directly to afflicted areas of the body" (Field of Invention) . Toppo only describes a 'transdermal delivery method will allow the drugs and/or medicaments to be delivered precisely into the body at specific area of pain" (Summary of Invention), meaning the area of pain origin. Nowhere does Toppo describe applying a topical NSAID to the keratinized skin of the head, nor does Toppo describe use of the compositions to relieve headache of any kind, let alone headache of central nervous system origin. There is no suggestion in Toppo to treat a headache of central nervous system origin by applying a composition topically to the keratinized skin surface of the head, as in the current claims.

Caldwell is directed to a pain relief composition whose active medicinal is a local anesthetic (abstract). Caldwell's teaching, therefore, is the treatment of headache using a specific topical *local anesthetic* formulation which penetrates the keratinized skin surface so as to directly interact with underlying specific nerves resulting in nerve impulse conduction blockade in the target nerves (col. 2, lines 46-51). *Local anesthetics* are a specific and distinct class of drugs that work by causing a reduction in nerve impulses by binding to sodium channels on the nerve (resulting in "numbness"), whereas NSAIDs reduce inflammation and do not bind to sodium channels. One of ordinary skill in the art would not extrapolate using the locally-applied nerve blocking agent in Caldwell to the teaching of the other references to topically apply an NSAID for treatment of central headaches as in the current claims. Moreover, the site of application of the topical local anesthetic formulation in Caldwell is very specific such that the formulation patented will penetrate the skin in several specific sites as described in the patent so as to interact with the supraorbital nerve and/or suboccipital nerve.

Accordingly, the combination of references fails to teach or suggest topically applying an anti-inflammatory effective amount of a topical NSAID formulation to a keratinized skin surface of the head to treat a headache of central nervous system origin, as claimed.

B) The Applicants further contend that the combination of the cited references fails to provide one of ordinary skill in the art with predicted success in the claimed invention.

The inventors of the present application found the unexpected and surprising results that, contrary to the accepted belief of those of ordinary skill in the art at the time the application was filed, one could treat the pain of *central* headaches, caused by migraine headache, indomethacin responsive headache syndrome, a tension headache, or cluster headache, by applying a *topical* NSAID formulation to a keratinized skin surface of the head.

The Applicants maintain that those of ordinary skill in the art would not have had a reasonable expectation of success in using a topical formulation of an NSAID applied to the keratinized skin surface of the head because (1) it was believed that the underlying pathophysiologic mechanism of migraines, indomethacin-responsive headaches, tension headaches, and cluster headaches were related to abnormalities deep within the brain; (2) it was known that topical formulations act locally and do not produce any significant drug levels in the systemic circulation nor in the brain; and (3) oral NSAIDs were known to successfully treat headache symptoms only if clinically significant systemic blood levels were achieved, as supported by the declaration provided by Dr. Newman. [4]

The Examiner has discounted Dr. Newman's declaration by alleging that the declaration was directed only to indomethacin responsive headaches and to one specific NSAID (indomethacin), and that therefore the declaration refers only to the "system described in the application and not to the individual claims" (Office Action of 11/4/2008, p. 13).

However, the Applicants respectfully disagree. The Applicants maintain that the claims are directed to topically applying an NSAID formulation, and that indomethacin is representative of the class of NSAIDs. Furthermore, as discussed in the previously cited declaration by Dr. Galer, an indomethacin responsive headache is representative of the class of primary headaches, as are migraine, cluster, and tension headaches.[5] In addition, the example cited in the original application demonstrated relief of migraine headache from topical diclofenac applied to the keratinized skin surface of the head.

Additionally, the Examiner has provided no reason to discount the declaration with respect to Claim 16, in which indomethacin is specified, or Claim 27, in which both indomethacin and an indomethacin responsive headache syndrome is specified.

C) The Applicants further contend that the Office has improperly combined Pradalier, Cluff, Toppo and Caldwell.

The Applicants maintain that the Office has used improper hindsight reasoning based on the disclosure in the Applicant's specification as the motivation to combine the references. The Applicants maintain that the Examiner's reasoning for combining the use of oral NSAIDs to treat migraine (Pradalier and Cluff) with a topical NSAID applied directly to afflicted areas of the body (Toppo) and the use of a local nerve blocking agent applied to the keratinized skin surface of the head to cause a nerve block and thus treat migraine (Caldwell) is not found in the prior art, and has in fact, been improperly derived from the Applicant's specification. As reasoned in the Board of Appeals decision

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[4] See the declaration of Dr. Lawrence Newman, dated 12-9-02, submitted with the Response to the Office Action of 12-18-2007.

[5] See International Classification of Headache Disorders, 2nd Edition; http://ihs-classification.org/en/; and Dodick , "Indomethacin-responsive Headache Syndromes.", abstract, from Exhibit A, enclosed in Response to Office Action of 3-30-06.

Ex Parte Robert J. Saccomanno, (Appeal 2008-4476; decided 11/ 21/08), "[T]he Examiner has not established that such reason would have been within the knowledge of one of ordinary skill in the art absent the Applicant's disclosure". In fact, as provided in the declaration by Dr. Newman, the Applicants maintain that it was thought that only clinically significant blood levels of any NSAID and indomethacin, for example, could successfully treat a central headache.

Nowhere except in the Applicant's specification is the teaching that a topically applied NSAID can be used to treat the head-pain of a central headache such as migraine. Furthermore, there would be no reason that one of ordinary skill in the art at the time of the invention would have used a topical NSAID applied to the keratinized skin surface of the head to treat a headache caused by a disturbance in the central nervous system. In fact, the Applicants maintain that it would not even be possible for one of ordinary skill in the art to use the method of topical application of NSAIDS to the 'afflicted area' as in Toppo to treat a central headache, for example, because this would mean applying the formulations of Toppo at a site of the affliction which is within the central nervous system, e.g within the brain [6], not to a keratinized skin surface of the head, as in the rejected claims. The pain that derives from arthritis is born directly within the joint and as such is easily conceived to be treated by a properly formulated topical NSAID, whereas as migraine and other centrally derived headache conditions are believed to be caused from abnormalities within the brain and as such, prior to this invention, would have not been conceived to be alleviated by a topical NSAID applied to the keratinized skin of the head.

Therefore, in view of the above discussion, the Applicants contend that the above references have been improperly combined, and furthermore, that the combination of references does not render the current claims obvious.

In light of the above discussion, it is submitted that: A) the combined teachings of the references fail to teach or suggest all elements of the claimed methods; B) the cited combination of references fails to provide the requisite predicted success in the claimed invention; and C) the cited prior art references have been improperly combined.

Accordingly, Claims 1-18 and 24-33 are not obvious under 35 U.S.C. § 103(a) over the combined teachings of either the article by Pradalier or the article by Cluff, each combined with both Caldwell and Toppo, and this rejection should be withdrawn.

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[6] A documented site of analgesic action of indomethacin in the case of some types of Indomethacin-responsive headaches. See Dodick, "Indomethacin-responsive Headache Syndromes.", p. 24, col. 2, from Exhibit A, enclosed in Response to Office Action of 3-30-06.

Applicants submit that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any fees under 37 C.F.R. §§1.16 and 1.17 which may be required by this paper, or to credit any overpayment, to Deposit Account No. 50-0815, reference no. TOPI-002CIP.

Respectfully submitted,

Date: February 11, 2009

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